Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 21, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.07.027

Selective Heart Rate Reduction With Ivabradine Unloads the Left Ventricle in Heart Failure Patients

Jan-Christian Reil, MD,* Jean-Claude Tardif, MD,† Ian Ford, MD,‡ Suzanne M. Lloyd, MSc,‡ Eileen O'Meara, MD,† Michel Komajda, MD,§ Jeffrey S. Borer, MD,|| Luigi Tavazzi, MD,¶ Karl Swedberg, MD,# Michael Böhm, MD*

Homburg/Saar, Germany; Montreal, Quebec, Canada; Glasgow, United Kingdom; Paris, France; Brooklyn and New York, New York; Cotignola, Italy; and Gothenburg, Sweden

Objectives The study aimed to determine whether isolated heart rate (HR) reduction with ivabradine reduces afterload of patients with systolic heart failure.

Background The effective arterial elastance (Ea) represents resistive and pulsatile afterload of the heart derived from the pressure volume relation. HR modulates Ea, and, therefore, afterload burden.

Methods Among the patients with systolic heart failure (ejection fraction ≤35%) randomized to either placebo or ivabradine in the SHIFT (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial), 275 patients (n = 132, placebo; n = 143, ivabradine 7.5 mg twice a day) were included in the echocardiographic substudy. Ea, total arterial compliance (TAC), and end-systolic elastance (Ees) were calculated at baseline and after 8 months of treatment. Blood pressure was measured by arm cuff; stroke volume (SV), ejection fraction, and end-diastolic volume were assessed by echocardiography.

Results At baseline Ea, TAC, HR, and Ees did not differ significantly between ivabradine- and placebo-treated patients. After 8 months of treatment, HR was significantly reduced in the ivabradine group ($p < 0.0001$) and was accompanied by marked reduction in Ea ($p < 0.0001$) and improved TAC ($p = 0.004$) compared with placebo. Although contractility remained unchanged, ventricular-arterial coupling was markedly improved ($p = 0.002$), resulting in a higher SV ($p < 0.0001$) in the ivabradine-treated patients.

Conclusions Isolated HR reduction by ivabradine improves TAC, thus reducing Ea. Because Ees is unaltered, improved ventricular-arterial coupling is responsible for increased SV. Therefore, unloading of the heart may contribute to the beneficial effect of isolated HR reduction in patients with systolic heart failure. (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial [SHIFT]; ISRCTN70429960) (J Am Coll Cardiol 2013;62:1977–85) © 2013 by the American College of Cardiology Foundation

Resting heart rate (HR) is directly related to adverse cardiovascular outcomes in patients with various cardiovascular diseases (1). We previously reported that isolated HR reduction with the I_f channel inhibitor ivabradine improves the composite endpoint of heart failure (HF) hospitalizations and cardiovascular death in patients with systolic HF in sinus rhythm who have a resting HR ≥70 beats/min before therapy (2,3), as well as improvement in quality of life (4). The benefits of HR reduction with ivabradine were directly related to the magnitude of HR reduction achieved by the drug and to the absolute value to which HR was

See page 1986

From *Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; †Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; ‡Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom; §Department of Cardiology, University Pierre et Marie Curie Paris VI, La Pitié-Salpétrière Hospital, Paris, France; ||Division of Cardiovascular Medicine and the Howard Gilman Institute for Heart Valve Disease, State University of New York Downstate Medical Center, Brooklyn and New York, New York; ¶Maria Cecilia Hospital, GVM Care and Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy; and the #Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. SHIFT was funded by Servier, Neuilly-sur-Seine, France. Dr. Tardif has a received research grant support from Servier. Dr. Borer has received honoraria and fees for serving as a consultant to Servier. Dr. Ford has received honoraria for serving is on the Steering Committee for trials run by Servier. Dr. Komajda has received honoraria from Servier for serving as a member of the Executive Committee of SHIFT and on the Speakers; is a Bureau. Dr. Tavazzi is an executive committee consultant for Servie; is a DSMB member for Cardiorentis; is on the Steering Committee for Viphor Pharma; is on the Events Adjudication Committee for St. Jude Medical; and is on Clinical Events Committee for Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 4, 2013; revised manuscript received June 26, 2013, accepted July 12, 2013.

Abbreviations and Acronyms

CO = cardiac output
Ea = effective arterial elastance
EDV = end-diastolic volume
Ees = end-systolic elastance
EF = ejection fraction
ESPVR = end-systolic pressure–volume relationship
HF = heart failure
HR = heart rate
LV = left ventricular
LVOT = left ventricular outflow tract
MAP = mean arterial pressure
Pes = end-systolic pressure
PP = pulse pressure
PV = pressure-volume
SV = stroke volume
TAC = total arterial compliance
TPR = total peripheral resistance

maximally reduced (3). These benefits were associated with left ventricular (LV) remodeling toward normal (5).

In experimental studies, HR reduction improves cardiac efficiency (6) and diastolic filling by prolonging diastole (7). Currently, it is unknown whether chronic HR reduction in humans also can reduce total afterload. Interestingly, the effective arterial elastance (Ea), integrating the mean and pulsatile load on the heart, directly depends on HR and total peripheral resistance (TPR) (8,9). Therefore, HR reduction may be directly associated with LV unloading (10). Furthermore, in animal models, ivabradine improves aortic distensibility by reducing vascular fibrosis and oxidative stress, resulting in improved ventricular-arterial interaction (10). Therefore, we hypothesized that isolated HR reduction with ivabradine reduces Ea by increasing vascular compliance, thereby unloading the left ventricle by improved ventricular-arterial interaction. This hypothesis was tested using data obtained from the subpopulation of the SHIFT (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial) who participated in the pre-specified echocardiographic substudy previously reported (5).

Methods

Study design. The design of the SHIFT was described in detail previously (2,3,11). Briefly, this randomized, double-blind, placebo-controlled, parallel-group, multinational clinical trial evaluated 6,505 male or female patients with moderate to severe chronic HF and documented LV systolic dysfunction (LV ejection fraction [EF] ≤35%). Eligible patients were in sinus rhythm with a resting HR of ≥70 beats/min on 12-lead electrocardiography; they had been clinically stable for ≥4 weeks and had been admitted to the hospital for worsening HF within the previous 12 months. HR and blood pressure were measured twice at 5-min intervals at 2 consecutive visits 2 weeks apart. All participants were receiving guidelines-based background therapy for HF, including maximized beta-blocker therapy, if tolerated. Other inclusion and exclusion criteria have been described previously (2,3,11). After a 2-week run-in period, patients were randomly assigned to receive either ivabradine (5 mg bid) or placebo. Randomization was stratified according to the dose of beta-blocker intake at randomization and country. At subsequent visits at 14 and 28 days and every 4 months thereafter (or at any other time if necessary), the dose of blinded study medication was increased to 7.5 mg bid or decreased to 2.5 mg bid depending on resting HR and tolerability. The SHIFT echocardiography substudy was performed at 89 centers in 21 countries participating in the main SHIFT. In total, the present analysis used 275 of the 411 patients of the SHIFT echocardiography substudy, specifically excluding those in the substudy who did not have both HR and stroke volume (SV) measured at the time of both echocardiographic measurements. To avoid selection bias, all the patients at each participating center were invited to enter the substudy, and the included patients signed a specific informed consent in addition to the documents related to the main study. The main study and substudy were approved by the local institutional review board at all participating centers. The substudy was carried out in accordance with the Declaration of Helsinki (1964) and its text revisions. The SHIFT is registered (ISRCTN70429960).

Definition of the Ea, total arterial compliance, and end-systolic elastance. Ea is a measure of both mean and pulsatile load, providing an integrated parameter reflecting the net impact of arterial vascular load on the heart (Fig. 1).

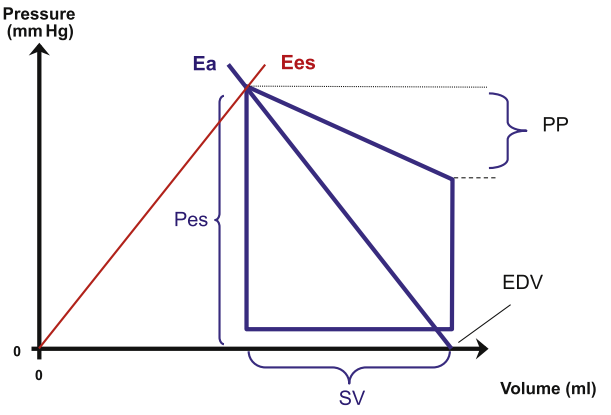

Figure 1 Scheme of a PV Diagram of the Left Ventricle

The blue squarelike figure represents a pressure-volume (PV) diagram of the left ventricle. Effective arterial elastance (Ea) is calculated by the end-systolic pressure (Pes) divided by stroke volume (SV) and represents the slope of the **blue line** connecting the end-systolic pressure volume point (Pes, ESV) and end-diastolic volume (EDV) on the x-axis. Ea represents both mean and pulsatile load to which the left ventricle is exposed. Total arterial compliance (TAC) is calculated by the ratio of SV divided by pulse pressure (PP = $P_{systolic}$-$P_{diastolic}$). TAC is a parameter of ventricular pulsatile load. The **red line** shows the ESPVR, which is mainly characterized by its slope Ees, a measure of cardiac contractility. It is calculated by the ratio of Pes and the ESV, referred to as the Sunagawa calculation. Ventricular-arterial coupling is defined by the coupling ratio of Ea/Ees. EF = ejection fraction; HR = heart rate; TPR = total peripheral resistance.

The index was introduced by Sunagawa et al. (12) in the 1980s and verified in humans by Kelly et al. (8). Ea is calculated by the ratio of end-systolic pressure (Pes) (mm Hg) and SV (ml) (8) (Fig. 1). Graphically, Ea can be depicted as the absolute value of the slope of a line linking the coordinate points of end-systolic volume (ESV) and the end-diastolic volume (EDV) (Fig. 1, red line). Ea is dependent on TPR and HR as follows:

TPR can be defined by the following equation:

$$TPR = (MAP - CVP)/CO \quad [1]$$

where MAP is the mean arterial pressure (mm Hg), CVP is the central venous pressure (mm Hg), and CO is cardiac output (l/min).

CO is defined by:

$$CO = SV \times HR \quad [2]$$

Substituting Equation 2 in Equation 1 results in:

$$TPR = (MAP - CVP)/(SV \times HR) \quad [3]$$

When assuming that CVP is stable and low compared with MAP and MAP is approximately equal to the Pes, Equation 3 can be recalculated as:

$$TPR \approx Pes/(SV \times HR), \quad [4]$$

where Pes = 0.9 × systolic blood pressure (mm Hg) measured by arm cuff (13). The term can be rearranged to:

$$TPR \times HR \approx Pes/SV \quad [5]$$

Pes/SV is per definition the Ea. Hence, Ea is dependent on HR and TPR.

The pulsatile load of the heart is defined by total arterial compliance (TAC) (Fig. 1). TAC is defined as the ratio of SV and pulse pressure (PP) (14): TAC = SV/PP. PP is calculated by the difference in systolic and diastolic pressure measured by arm cuff.

LV end-systolic elastance (Ees) is the slope of the end-systolic pressure-volume relationship ESPVR and represents LV contractility (12) (Fig. 1). Normally it can only be calculated invasively by reducing the preload when using a pressure-volume (PV) conductance catheter. However, it can also be derived echocardiographically by single-beat analysis. Two different methods for Ees calculation were performed.

According to Sunagawa et al. (12) and Schwartzenberg et al. (15), Ees can be calculated by the ratio of the Pes and the end-systolic volume, assuming the x-axis intercept of ESPVR $V_0 = 0$. The equation was used in experimental studies (12) and in patients with HF (15) This formula was calculated in 134 ivabradine-treated patients and 128 placebo-treated patients: Ees = Pes/ESV.

According to Chen et al. (16), single-beat Ees can be assessed using an algorithm containing systolic and diastolic blood pressure, SV, EF, and pre-ejection and total systolic ejection time intervals from LV outflow Doppler. This formula was also calculated in patients receiving placebo or ivabradine treatment equipped with a complete dataset (n = 41 per group).

Ventricular-arterial interaction can be assessed by the ratio Ea/Ees in the pressure volume diagram and is defined as the coupling ratio.

Echocardiographic imaging and blood pressure measurements. Echocardiography was performed at baseline (in the 2 weeks between selection and inclusion) and within 1 month of the 8-month visit. Echocardiographic recordings were carried out according to a pre-defined operational protocol and read blindly and centrally in the core laboratory at the Montreal Heart Institute. The 2 recordings were to be made by the same technician using the same technique and the same equipment. Transthoracic echocardiography was performed with a phased-array imaging system equipped with a transducer with second harmonics capability. Images were obtained in the parasternal long- and short-axis and apical views, with the subject lying in the left lateral position (for details, see Tardif et al. [5]). To quantify SV, the LV outflow tract (LVOT) time velocity integral was measured by pulsed-wave Doppler in the apical 5-chamber view and LVOT diameter d was measured in the parasternal long-axis view.

$$\text{SV was assessed by} = \text{LVOT time velocity integral} \times (d/2)^2 \times 3.14$$

Blood pressure was measured by an arm cuff system in sitting position after a 5-min rest. LV EDV and EF were measured by using the modified Simpson rule or Dumesnil formula.

Statistics. Summary statistics are reported as mean (SD) for continuous variables and as number (%) for categorical variables. Differences between treatment groups at baseline were analyzed using 2-sample *t* tests for continuous variables and chi-square tests for categorical variables; p values from these tests are reported. Associations between HR and the hemodynamic parameters at baseline were also investigated. For presentation purposes, the hemodynamic parameters are presented by tertiles of HR; p values from analysis of variance models for tests for trends are also reported.

Echocardiographic, blood pressure, and hemodynamic parameters are summarized by treatment group at baseline and month 8; the change from baseline (month 8 − baseline) values are also reported. Analysis of variance models were used to test for differences between the treatment groups at each time point (and change from baseline) and paired *t* tests to test for differences within each group over time.

Associations between the EF and coupling ratio at baseline and for the change from baseline were analyzed using scatterplots and correlation coefficients.

Values $p < 0.05$ were considered to reflect statistically significant differences. All analyses were carried out using

JACC Vol. 62, No. 21, 2013
November 19/26, 2013:1977–85

SAS for Windows version 9.2 (SAS Institute, Cary, North Carolina).

Results

Of the 275 patients involved in this analysis, 143 were treated with ivabradine and 132 with placebo. Table 1 summarizes the demographic and clinical data of both groups at substudy entry. Patients from the 2 study arms did not differ significantly with respect to the listed parameters.

When the study population was subdivided into tertiles of HR at baseline, TAC decreased with higher HR, whereas Ea significantly increased (Table 2, Fig. 2). PP and Pes remained largely unchanged, whereas SV significantly decreased with increasing HR (Table 2). Increase in Ea and reduction of TAC were mainly dependent on decreased SV. Pes and PP remained relatively unchanged as HR increased (Table 2).

The effect of isolated HR reduction on LV hemodynamics and ventricular-arterial coupling at baseline and after 8 months of ivabradine treatment is summarized in Table 3. At baseline, heart rate hemodynamic and coupling parameters did not differ significantly between the ivabradine and placebo groups. Accordingly, EDV was similar in both groups (Table 3).

After 8 months, ivabradine-treated patients showed a significantly decreased HR compared with controls. PP, MAP, and Pes in the placebo and ivabradine groups did not differ significantly (Table 3). HR reduction was accompanied by a significant increase in SV in the ivabradine group. This change was associated with a significant increase in TAC and a decrease in Ea compared with placebo. TPR did not differ between both groups. LV EDV was significantly reduced in the ivabradine group after 8 months of treatment compared with baseline (leftward shift of the PV loop) (Table 3) but showed no significant difference compared with placebo. Nevertheless, both the relative and absolute reductions of EDV were significantly increased compared with placebo. Additionally, Ees, describing LV contractility, showed no significant difference in the ivabradine or placebo group based on both calculations (Table 3). The coupling ratio Ea/Ees, representing vascular-ventricular interaction, was similar at baseline in the 2 groups. After 8 months, the Ea/Ees ratio decreased significantly in the ivabradine group ($p < 0.01$) (Table 3) and compared with the placebo group ($p < 0.001$). Additionally, a strong inverse correlation between EF and the coupling ratio Ea/Ees ($r = -0.77$, $p < 0.001$) (Fig. 3) as well as the change in coupling ratio and change in EF in the ivabradine-treated patients ($r = -0.63$, $p < 0.001$) and placebo-treated patients ($r = -0.61$, $p < 0.001$) could be detected. Notably, there was no significant correlation between Ea and Ees at baseline ($r = -0.07$, $p = 0.22$).

Table 1 Basic Characteristics of Both Groups at Baseline

	All (N = 275)	Ivabradine (n = 143)	Placebo (n = 132)	p Value
Demographic characteristics				
Age, yrs	59.7 (11.1)	60 (10.8)	59.4 (11.5)	0.65
Male	224 (81.5)	119 (83.2)	105 (79.5)	0.43
Clinical data				
NYHA functional class II	153 (55.6)	82 (57.3)	71 (53.8	0.55
NYHA functional class III+IV	122 (44.4)	61 (42.7)	61 (46.2)	
Heart rate, beats/min	71 (11.4)	71 (11.8)	71 (11.0)	0.70
Systolic blood pressure, mm Hg	122 (15)	123 (15.7)	121 (14.2)	0.33
Diastolic blood pressure, mm Hg	76 (8.6)	76 (9.2)	76 (8.0)	0.81
Medical history				
Current smoker	45 (16.4)	29 (20.3)	16 (12.1)	0.07
Diabetes	85 (30.9)	42 (29.4)	43 (32.6)	0.57
Hyperlipidemia	39 (14.2)	23 (16.1)	16 (12.1)	0.35
CAD	197 (71.6)	105 (73.4)	92 (69.7)	0.49
Previous MI	165 (60.0)	90 (62.9)	75 (56.8)	0.30
Coronary artery surgery	42 (15.3)	22 (15.4)	20 (15.2)	0.95
Stroke	23 (8.4)	13 (9.1)	10 (7.6)	0.65
Drugs				
Diuretics	238 (86.5)	126 (88.1)	112 (84.8)	0.43
Beta-blocker	257 (93.5)	135 (94.4)	122 (92.4)	0.51
ACE inhibitor	216 (78.5)	114 (79.7)	102 (77.3)	0.62
ARB	42 (15.3)	24 (16.8)	18 (13.6)	0.47
Lipid-lowering agents	190 (69.1)	99 (69.2)	91 (68.9)	0.96
Cardiac glycosides	56 (20.4)	28 (19.6)	28 (21.2)	0.74
Renal function				
Creatinine, μmol/l	98 (23.2)	99 (25.5)	97 (20.4)	0.44

Values are mean (SD) or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; MI = myocardial infarction; NYHA = New York Heart Association.

Table 2 Heart Rate Subdivided in Tertiles and Hemodynamic Parameters at Baseline

Hemodynamics	1st Tertile HR <65 beats/min (n = 93)	2nd Tertile 65 ≤ HR ≤75 beats/min (n = 91)	3rd Tertile HR >75 beats/min (n = 91)	p Value*
Pes, mm Hg	110 ± 13	109 ± 13	111 ± 14	0.55
Pulse pressure, mm Hg	48 ± 12	45 ± 11	46 ± 12	0.31
Stroke volume, ml	64 ± 14	60 ± 16	53 ± 15	<0.001
Total arterial compliance, ml/mm Hg	1.5 ± 0.6	1.4 ± 0.5	1.2 ± 0.4	<0.001
Effective arterial elastance, mm Hg/ml	1.8 ± 0.5	1.9 ± 0.5	2.3 ± 0.7	<0.001

Values are mean ± SD. *p value from tests for trend.

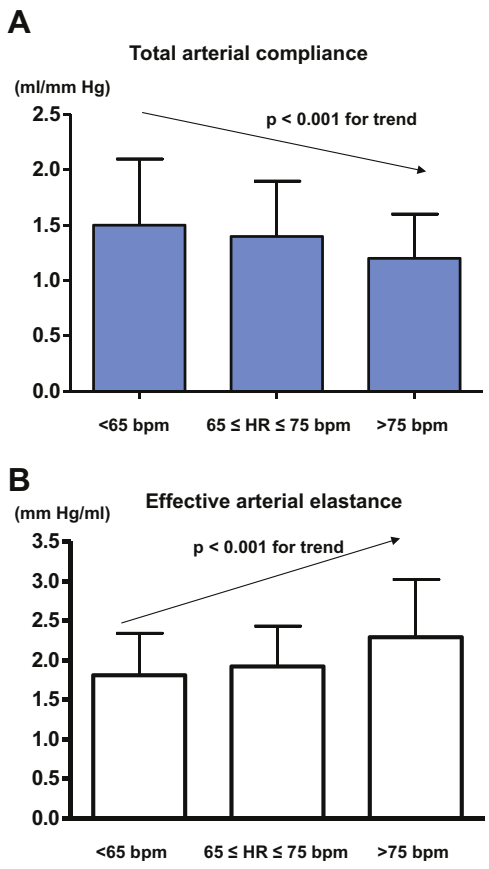

Figure 2 Arterial Compliance and Elastance Graphs

(A) Total arterial compliance and heart rate subdivided in tertiles. **(B)** Effective arterial elastance and heart rate (HR) subdivided in tertiles.

Interestingly, CO was maintained in the ivabradine group compared with the placebo group after 8 months of treatment.

Discussion

The influence of HR on afterload burden was investigated in a cohort of patients with systolic HF. Isolated HR reduction with ivabradine significantly reduced Ea, a parameter representing the pulsatile and mean load of the left ventricle. This reduction of total afterload is mainly triggered by a decrease in vascular pulsatile load indicated by increased TAC, whereas systemic vascular resistance remained constant. Improved TAC resulted in improved ventricular-arterial coupling with a significant increase in SV without changes in LV contractility and CO.

HR and vascular function. The mutual interaction of HR and Ea has been demonstrated experimentally in isolated canine hearts at constant preload and impedance (12), and in closed-chest dogs (17). In addition, this relation has been seen in investigations in humans (8). Beside the study of Maurer et al. (18) investigating the influence of carvedilol on HR reduction and EF in heart failure with reduced ejection fraction patients, this is the only study in which HR dependency of Ea was investigated in the setting of long-term treatment of humans. The apparent improvement in TAC in this study is consistent with experimental and other clinical data. In rats, increases in HR produced by atrial pacing have been associated with a marked decrease in carotid artery compliance (19). Similarly, HR has been directly related to arterial stiffness in the central and lower limb arteries (20) as well as in radial and carotid arteries of humans (21). Interestingly, isolated HR reduction by ivabradine was found to mediate antihypertrophic effects in the thoracic aorta of rats as measured by a reduction of media cross-sectional area; this alteration, in turn, reduced vascular wall stress (22). Also, it has been shown experimentally that isolated HR reduction with ivabradine improves aortic distensibility by reducing aortic fibrosis and oxidative stress (10). However, in contrast to long-term treatment, acute short-term repetitive intravenous administration of ivabradine did not affect arterial stiffness (23). These findings suggest that blood vessels can adapt to increased mechanical wall stress by changing their tissue structure, elastic properties, and geometry, possibly beneficially influenced by HR reduction.

HR reduction and ventricular-arterial interaction. Ventricular systolic and diastolic function as well as vascular tone and compliance determine blood pressure and peripheral flow (13,24,25). In the PV relationship, ventricular systolic performance is understood to be represented by the Ees, whereas arterial function and afterload are characterized by Ea (8,12). The coupling ratio Ea/Ees was introduced to describe and evaluate ventricular-arterial interaction (13,25,26). Ees and Ea are matched in healthy persons to provide optimal transition of SV to the peripheral circulation. Experimentally, the specific margin of the coupling ratio Ea/Ees was 0.6 to 1.2 when work and efficiency of myocardial function were optimal (27).

Ea and Ees increase with aging in both men and women (28). Compared with the corresponding values of healthy individuals 60 years of age (28,29), measured parameters of the investigated patients were typical of the values found in systolic HF (Table 3). These patients demonstrated a rightward shift in the PV loop due to increased EDV and Ea, whereas Ees considerably decreased compared with healthy matched individuals (Fig. 4). The latter parameters resulted in an abnormally high coupling ratio (24,25) leading to decreased cardiac efficiency (30).

Similar to vasodilator therapy (15), HR reduction by ivabradine reduced Ea, thereby improving ventricular-arterial interaction. Due to a flat Ees curve in the PV relationship of patients with systolic HF (Fig. 4), reduction of Ea is accompanied by a relative increase in SV, whereas end-systolic blood pressure remains nearly unchanged (15,25). However, no significant changes in Ees values (LV contractility) were demonstrated between the groups. These results agree with experimental studies reporting that LV contractility was not influenced by ivabradine (31), except in high concentrations (32) far beyond what might be achieved clinically.

JACC Vol. 62, No. 21, 2013
November 19/26, 2013:1977–85

Table 3 Influence of Selective Heart Rate Reduction With Ivabradine on Hemodynamic Parameters After 8 Months of Treatment Compared With Placebo

Parameter	Ivabradine (n = 143)	Placebo (n = 132)	p Value
Heart rate, beats/min			
At baseline	71 ± 12	71 ± 11.0	0.71
At 8 months	60 ± 10	68 ± 12	<0.0001
Change from baseline to 8 months	−11 ± 13	−2 ± 12	<0.0001
p Value vs. baseline	<0.0001	0.015	
Pulse pressure, mm Hg			
At baseline	47 ± 12	45 ± 11	0.28
At 8 months	49 ± 14	48 ± 13	0.51
Change from baseline to 8 months	2 ± 13	3 ± 11	0.75
p Value vs. baseline	0.03	0.005	
End-systolic pressure, mm Hg			
At baseline	111 ± 14	109 ± 13	0.33
At 8 months	113 ± 15	112 ± 14	0.56
Change from baseline to 8 months	2 ± 14	3 ± 13	0.72
p Value vs. baseline	0.04	0.006	
MAP, mm Hg			
At baseline	91.6 ± 10.3	90.8 ± 9.1	0.51
At 8 months	92.8 ± 10.5	92.4 ± 10.4	0.73
Change from baseline to 8 months	1.2 ± 10.7	1.5 ± 10.3	0.80
p Value vs. baseline	0.18	0.09	
Stroke volume, ml			
At baseline	59 ± 16	59 ± 16	0.80
At 8 months	67 ± 16	58 ± 16	<0.0001
Change from baseline to 8 months	9 ± 17	−1 ± 16	<0.0001
p Value vs. baseline	<0.0001	0.39	
Total arterial compliance, ml/mm Hg			
At baseline	1.35 ± 0.53	1.38 ± 0.48	0.62
At 8 months	1.49 ± 0.58	1.30 ± 0.51	0.004
Change from baseline to 8 months	0.14 ± 0.59	−0.08 ± 0.48	<0.001
p Value vs. baseline	0.005	0.06	
Effective arterial elastance, mm Hg/ml			
At baseline	2.04 ± 0.69	1.96 ± 0.55	0.29
At 8 months	1.78 ± 0.54	2.06 ± 0.59	<0.0001
Change from baseline to 8 months	−0.26 ± 0.68	0.10 ± 0.58	<0.0001
p Value vs. baseline	<0.0001	0.04	
Total peripheral resistance, mm Hg/ml			
At baseline	0.02 ± 0.01	0.02 ± 0.01	0.59
At 8 months	0.02 ± 0.01	0.03 ± 0.01	0.53
Change from baseline to 8 months	0.00 ± 0.01	0.00 ± 0.01	0.27
p Value vs. baseline	0.18	0.001	

Continued on the next page

A decrease in EDV was identified in the ivabradine-treated patients (Table 3). The decrease in EDV might be induced by improved ventricular-arterial coupling due to decreased Ea. The leftward shift of the PV loop to smaller EDV values of ivabradine-treated patients can be interpreted as reverse remodeling (Fig. 4A). The Ea-elicited change is in accordance with the data of the echocardiographic main study of the SHIFT (5). Summing up, improved ventricular-arterial interaction caused by HR reduction seems to contribute to the increase in SV and improved cardiac efficiency, thereby preserving CO of patients receiving ivabradine. Accordingly, CO was maintained after acute intravenous administration of ivabradine in patients with systolic HF (33).

Study limitations. Blood pressure measurements of this study were performed noninvasively by an arm cuff system. Therefore, measurements could overestimate central blood pressure in both groups because brachial artery pressure is normally higher than aortic pressure due to central pressure wave amplification (34,35). Central blood pressure, however, is also increased due to reflected pressure waves. This increase is influenced by HR as well because lower HRs improve synchronization of the forward and backward traveling waves, resulting in higher central PPs (35). Therefore, ivabradine-treated patients with HR reduction of ~10 beats/min may have had slightly higher central systolic blood pressure levels compared with controls,

Table 3 Continued

Parameter	Ivabradine (n = 143)	Placebo (n = 132)	p Value
Cardiac output, ml/min	n = 134	n = 128	
At baseline	4,091 ± 1,029	4,123 ± 1,074	0.80
At 8 months	3,992 ± 978	3,868 ± 979	0.30
Change from baseline to 8 months	−100 ± 1,159	−254 ± 1,006	0.24
p Value vs. baseline	0.31	<0.01	
Calculation according to Sunagawa et al. (12)			
End-systolic elastance, mm Hg/ml	n = 134	n = 128	
At baseline	1.08 ± 0.58	1.13 ± 0.64	0.45
At 8 months	1.30 ± 0.71	1.20 ± 0.67	0.25
Change from baseline to 8 months	0.22 ± 0.46	0.07 ± 0.43	0.005
p Value vs. baseline	<0.0001	0.08	
Effective arterial elastance/end-systolic elastance	n = 134	n = 128	
At baseline	2.43 ± 1.55	2.34 ± 1.55	0.65
At 8 months	1.80 ± 1.09	2.30 ± 1.44	0.002
Change from baseline to 8 months	−0.63 ± 1.30	0.04 ± 1.21	<0.0001
p Value vs. baseline	<0.0001	0.69	
Ejection fraction	n = 134	n = 128	
At baseline	0.32 ± 0.10	0.33 ± 0.11	0.88
At 8 months	0.36 ± 0.12	0.33 ± 0.11	0.03
Change from baseline to 8 months	0.04 ± 0.10	0.01 ± 0.09	0.004
p Value vs. baseline	<0.0001	0.41	
End-systolic volume, ml	n = 143	n = 132	
At baseline	126.6 ± 57.2	123.3 ± 61	0.65
At 8 months	110.7 ± 56.7	119.1 ± 57	0.23
Change from baseline to 8 months	−15.9 ± 37.9	−4.2 ± 38.7	0.01
p-value vs. baseline	<0.0001	0.23	
End-diastolic volume, ml	n = 134	n = 128	
At baseline	181 ± 62	176 ± 65	0.51
At 8 months	167 ± 59	172 ± 62	0.46
Change from baseline to 8 months	−15 ± 40	−4 ± 42	0.04
p Value vs. baseline	<0.0001	0.29	
Relative change, %	−5.9 ± 20	0.7 ± 24	0.01
Calculation according to Chen et al. (16)			
End-systolic elastance, mm Hg/ml	n = 41	n = 41	
At baseline	1.36 ± 0.44	1.43 ± 0.45	0.47
At 8 months	1.32 ± 0.49	1.36 ± 0.45	0.74
Change from baseline to 8 months	−0.03 ± 0.44	−0.07 ± 0.43	0.69
p Value vs. baseline	0.6	0.3	
V_0, ml	n = 41	n = 41	
At baseline	37 ± 51	57 ± 68	0.14
At 8 months	12 ± 56	38 ± 55	0.04
Change from baseline to 8 months	−25 ± 47	−19 ± 54	0.61
p Value vs. baseline	0.002	0.03	
Effective arterial elastance/end-systolic elastance	n = 41	n = 41	
At baseline	1.50 ± 0.53	1.45 ± 0.38	0.62
At 8 months	1.38 ± 0.39	1.57 ± 0.49	0.06
Change from baseline to 8 months	−0.13 ± 0.46	0.11 ± 0.43	0.02
p Value vs. baseline	0.09	0.10	

Values are mean ± SD.

which cannot be ruled out by the brachial artery measurement.

Because the Ees calculation according to Sunagawa et al. (12) supposes an x-axis intercept of $V_0 = 0$ of ESPVR, Ees was alternatively calculated according to Chen et al. (16) in a subgroup of 41 patients. The Chen et al. (16) calculation was shown to be a reliable estimate of invasive measurements assuming $V_0 \neq 0$ (16). Confirming the results of the Sunagawa et al. Ees calculation, the Chen et al. technique showed no significant difference for Ees values within and

JACC Vol. 62, No. 21, 2013
November 19/26, 2013:1977–85

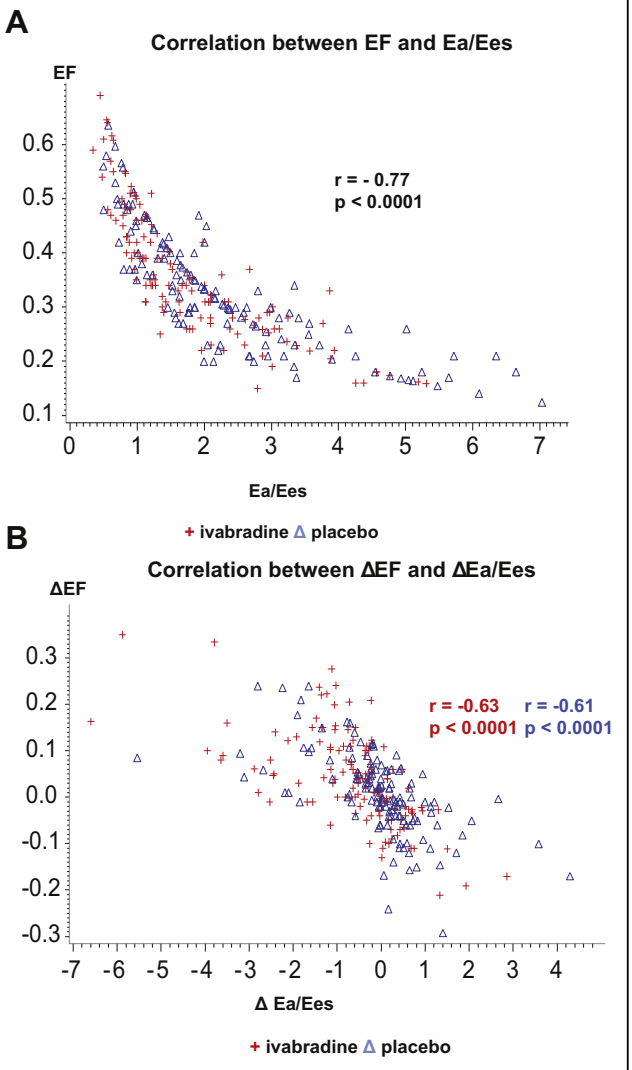

Figure 3 Correlation Curves

(A) Scatterplot for the correlation between EF and Ea/Ees. **(B)** Scatterplot for the correlation between ΔEF and ΔEa/Ees. Abbreviations as in Figure 1.

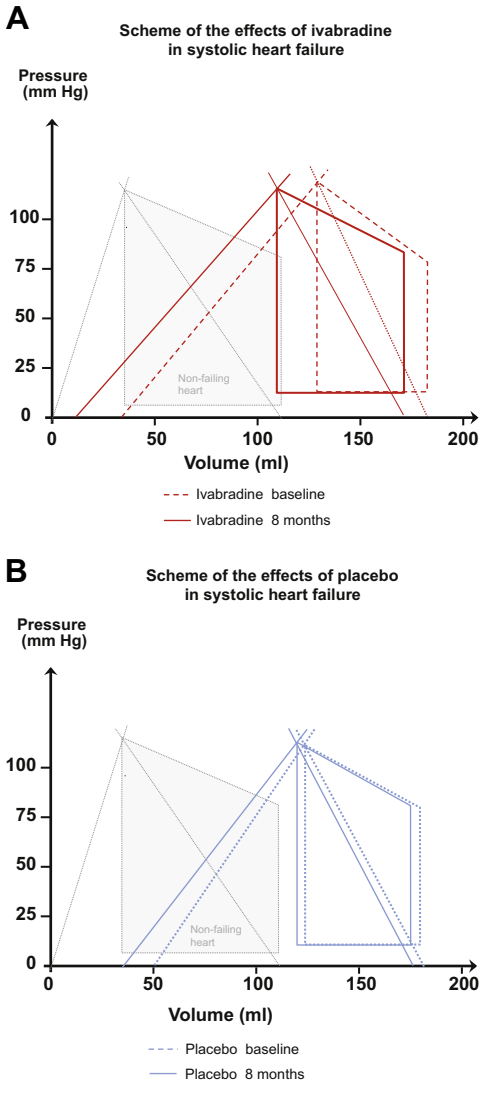

Figure 4 Schematic Pressure-Volume Loops

Schematic pressure-volume diagrams of the left ventricle in the ivabradine group **(red loops, A)** and placebo **(blue loops, B)** at baseline **(dotted blue or red loop)** and after 8 months of treatment **(solid red or blue loop)** compared with a non-failing control **(gray loop)**. Systolic heart failure is indicated by an increase in EDV, flat end-systolic elastance, reduced SV, and increased Ea in both groups **(red and blue dotted loop)**. Ivabradine treatment over 8 months reduced afterload (Ea), thereby improving ventricular-arterial interaction with marked increase in SV compared with placebo **(red solid loop)**. Contractility indicated by Ees (Chen calculation) in the ivabradine group **(red ascending lines)** did not differ significantly compared with that of the placebo group **(blue ascending lines)**. Noticeable is the prominent leftward shift of the x-axis intercept of ESPVR of the ivabradine group **(solid vs. dotted lines)** indicating reverse remodeling. Placebo treatment did not alter afterload, resulting in approximately congruent loops (blue dotted and solid loop). Abbreviations as in Figure 1.

between both groups. The x-axis intersection V_0 of ivabradine-treated patients, however, was significantly shifted to the left compared with the placebo group. The leftward shift of ESPVR can be interpreted as reverse remodeling, whereas contractility (Ees) remained nearly unchanged. This shift might also explain the inherent disparity between Ees change in both calculations after ivabradine treatment (Sunagawa Ees increased, Chen Ees decreased by trend). The Sunagawa Ees steepened within the ivabradine group more than that in the placebo group after 8 months of treatment because the Sunagawa et al. Ees does not account for V_0, whereas V_0 of the Chen calculation decreased consistent with reverse remodeling. Therefore, the measured increase in Ees (Sunagawa) in the ivabradine-treated patients (Table 3) does not reflect actual increase in contractility but depends on the defined mathematical specification.

In this study, no direct and therefore no invasive measures of vascular structure and function were performed but should be done in the future to confirm the presented results.

Conclusions

HR modulates cardiac afterload in chronic systolic HF, as indicated by the alterations of Ea demonstrated in patients from the SHIFT. Selective HR reduction with ivabradine improved TAC, thus reducing Ea with improvement of ventricular-arterial coupling. Because Ees, a marker of LV contractility, remained unchanged, increased ventricular-arterial coupling must be assumed to have produced the increased SV seen in ivabradine-treated patients. Therefore, unloading of the heart has been demonstrated as an underlying hemodynamic mechanism of isolated HR reduction and may contribute to the beneficial outcome of ivabradine-treated patients with systolic HF.

Acknowledgment

The authors thank G.-H. Reil for helpful and important discussion of the manuscript.

Reprint requests and correspondence: Dr. Jan-Christian Reil, Klinik für Innere Medizin III (Kardiologie, Angiologie, Internistische Intensivmedizin), Universitätsklinikum des Saarlandes, Kirrberger Straße, D 66421 Homburg/Saar, Germany. E-mail: jan.reil@uks.eu.

REFERENCES

1. Reil JC, Custodis F, Swedberg K, et al. Heart rate reduction in cardiovascular disease and therapy. Clin Res Cardiol 2011;100:11–9.
2. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized, placebo-controlled study. Lancet 2010;376:875–85.
3. Böhm M, Swedberg K, Komajda M, et al., for the SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886–94.
4. Ekman I, Chassany O, Komajda M, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J 2011;32:2395–404.
5. Tardif JC, O'Meara E, Komajda M, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. Eur Heart J 2011; 32:2507–55.
6. Colin P, Ghaleh B, Monnet X, Hittinger L, Berdeaux A. Effect of graded heart rate reduction with ivabradine on myocardial oxygen consumption and diastolic time in exercising dogs. J Pharmacol Exp Ther 2004;308:236–40.
7. Mulder P, Barbier S, Chagraoui A, et al. Long-term heart rate reduction induced by the selective I(f) current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. Circulation 2004;109:1674–9.
8. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513–21.
9. Reil JC, Reil GH, Böhm M. Heart rate reduction by I(f)-channel inhibition and its potential role in heart failure with reduced and preserved ejection fraction. Trends Cardiovasc Med 2009;19:152–7.
10. Reil JC, Hohl M, Reil GH, et al. Heart rate reduction by If-inhibition improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of heart failure with preserved ejection fraction. Eur Heart J 2013;34:2839–49.
11. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail 2010;12:75–81.
12. Sunagawa K, Maughan WL, Burkhoff D, Segawa K. Left ventricular interaction with arterial load studied in the isolated canine ventricle. Am J Physiol 1983;245:H773–80.
13. Borlaug BA, Lam CSP, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease. J Am Coll Cardiol 2009;54:410–8.
14. Chemla D, Hebert JL, Coirault C, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274:H500–5.
15. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol 2012;59:442–51.
16. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028–34.
17. Freeman GL, Colston JT. Role of ventriculovascular coupling in cardiac response to increased contractility in closed-chest dogs. J Clin Invest 1990;86:1278–84.
18. Maurer MS, Sackner-Bernstein JD, El-Khoury Rumbarger L, Yushak M, King DL, Burkhoff D. Mechanisms underlying improvements in ejection fraction with carvedilol in heart failure. Circ Heart Fail 2009;2:189–96.
19. Mangoni AA, Mircoli L, Giannattasio C, Ferrari AU, Mancia G. Heart rate-dependence of arterial distensibility in vivo. J Hypertens 1996;14:897–901.
20. Sa Cunha R, Pannier B, Benetos A, et al. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. J Hypertens 1997;15:1423–30.
21. Giannattasio C, Vincenti A, Failla M, et al. Effects of heart rate changes on arterial distensibility in humans. Hypertension 2003;42: 253–6.
22. Albaladejo P, Carusi A, Apartian A, Lacolley P, Safar ME, Benetos A. Effect of chronic heart rate reduction with ivabradine on carotid and aortic structure and function in normotensive and hypertensive rats. J Vasc Res 2003;40:320–8.
23. Albaladejo P, Challande P, Kakou A, et al. Selective reduction of heart rate by ivabradine: effect on the visco-elastic arterial properties in rats. J Hypertens 2004;22:1739–45.
24. Borlaug BA, Kass DA. Invasive hemodynamic assessment in heart failure. Heart Failure Clin 2009;5:217–28.
25. Borlaug BA, Kass DA. Vascular-ventricular interaction in heart failure. Heart Failure Clin 2008;4:23–36.
26. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–20.
27. de Tombe PP, Jones S, Burckhoff D, Hunter WC, Kass DA. Ventricular stroke work and efficiency remain nearly optimal despite altered vascular loading. Am J Physiol 1993;264:H1817–24.
28. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age-and gender-related ventricular-vascular stiffening. Circulation 2005;112:2254–62.
29. OH JK, Seward JB, Tajik AJ. The Echo Manual. 3rd edition. Philadelphia, PA: Lippincott–Raven, 2004:403.
30. Asanoi H, Sasayama S, Kameyama T. Ventriculo-arterial coupling in normal and failing heart in humans. Circ Res 1989;65:483–93.
31. Di Francesco D, Camm JA. Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. Drugs 2004;64:1757–65.
32. Boldt A, Gergs U, Ponicke K, Simm A, Silber RE, Neumann J. Inotropic effects of ivabradine in the mammalian heart. Pharmacology 2010;86:249–58.
33. De Ferrari GM, Mazzuero A, Agnesina L, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart F 2008;10:550–5.
34. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213–25.
35. Safar ME, Protogerou AD, Blacher J. Statins, central blood pressure, and blood pressure amplification. Circulation 2009;119:9–12.

Key Words: heart rate reduction ■ systolic heart failure ■ ventricular-arterial coupling.